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Comments on FDA Draft Guidance Document for *In Vivo* Cervical Devices
Guidance for Industry: Electro-optical Sensors for the In Vivo Detection of Cervical Precancer and its Precursors: Submission Guidance for an IDE/PMA
[Docket No. 99D-2211]

Dear Mr. Pollard and Dr. Virmani:

We wish to comment on some aspects of the recent revision of the FDA guidance document for *in vivo* cervical devices. The guidance document outlines some of the aspects of clinical trials that would be required for various indications for use.

Although we have comments on several aspects of the document, we are most concerned with the examples of cytological sensitivity given on page 16, which could be interpreted as the agency's determination of Pap smear accuracy. The available data on the accuracy of the Pap smear shows a much lower level than that suggested in the guidance document. As a result, if the examples given in the document were taken as targets for study results, they would establish a requirement that cannot be attained either by cytology or new *in vivo* cervical devices. We suggest that since the accuracy of cytology is very setting dependent, you consider not quoting an absolute accuracy.

This letter is divided into three main sections - the first section concentrates on the sensitivity and specificity targets, the second section recommends consideration of the use of an *in study* Pap smear for the triage indication and the third section comprises our other comments on the document.

99D-2211

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1.1 Guidance Document Statement

On page 16 of the guidance document in the section entitled 'Primary Screening Device as an Alternative to Cervical/Vaginal Cytology', the document states:

> *"Sponsor should quantify the improvement in sensitivity or specificity targeted as a goal and the 'clinically significant decrease' in the other measures targeted to be avoided...For example, the sponsor might target an improvement in sensitivity of at least 5%, above the expected sensitivity of 85% without the in vivo device, while not reducing the specificity of the in vivo device by more than 3 percent."*

Given the context of the above paragraph (i.e. within a section about replacement of cytology by *in vivo* device screening), many may interpret it to mean that cytology is expected to reach a sensitivity of 85% and that the *in vivo* device must reach at least 90% sensitivity, while specificity compared to cytology must decrease only by a maximum of 3%. Our concern relates to our belief that the sensitivity of the Pap smear is not as high as 85%. We realize that the figures in the FDA document are given as examples only, however we are worried that they imply, or may set a precedent for, an inappropriate benchmark for cytology as well as for new *in vivo* cervical devices.

We suggest that the paragraph be re-worded as follows:

> *"Sponsor should quantify the improvement in sensitivity or specificity targeted as a goal and the 'clinically significant decrease' in the other measures targeted to be avoided...For example, the sponsor might target an improvement in sensitivity of at least 5 percent above that demonstrated by in study cytology, while not reducing the specificity of the in vivo device by more than 3 percent."*

1.2 Pap Accuracy Considerations

The following section summarizes the available data and considerations regarding Pap smear accuracy. The two most comprehensive studies on Pap smear accuracy are both meta-analyses of a large number of studies.[1,2] Both studies summarize the accuracy of cytology using the Receiver Operating Characteristic (ROC) curve.

[1] Fahey MT, Irwig L and Macaskill P, Meta-analysis of Pap test accuracy, *American Journal of Epidemiology* 1995: 141(7); 680-9.

[2] Evidence Report/Technology Assessment Number 5: *Evaluation of Cervical Cytology*. Agency for Health Care Policy and Research. AHCPR Publication No. 99-E010, February 1999.

1.2.1. The Receiver Operating Characteristic (ROC) Curve

The ROC is a graphic representation of the trade-off between sensitivity and specificity as the test threshold varies (Figure 1).

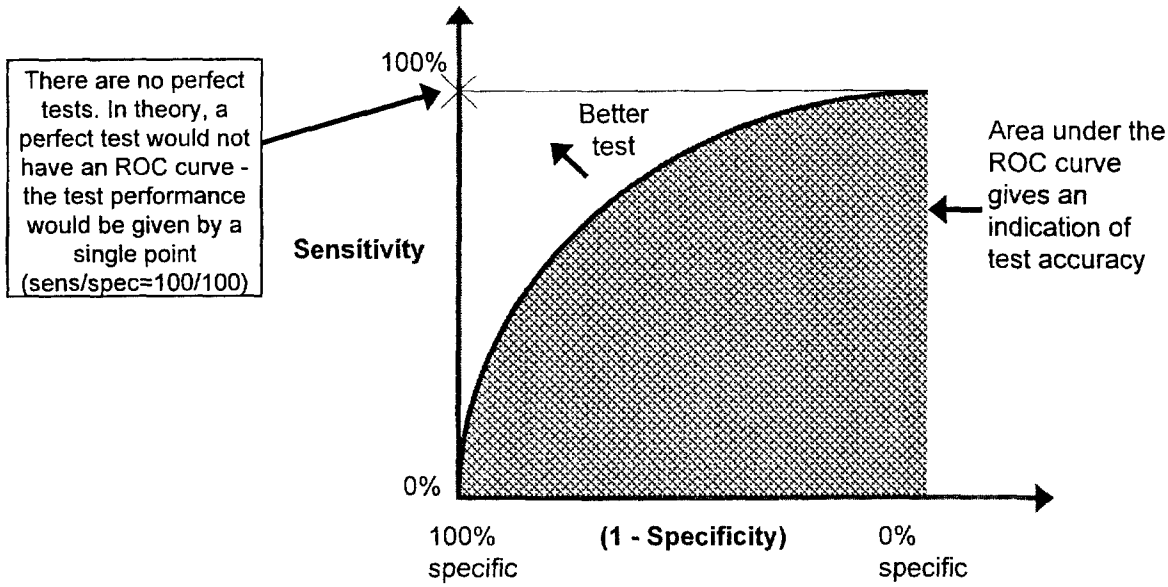

Figure 1. The Receiver Operating Characteristic (ROC) Curve

The ROC is a convenient means of summarizing the accuracy of a test under a variety of conditions, and ROC curves are commonly produced for various screening tests. As an example, an ROC curve for the Prostate Specific Antigen (PSA) test for prostate cancer is reproduced as Figure 2.[3] This ROC is based on the results of a 6,630 patient study and shows that at the commonly used PSA threshold of 4 ng/mL, the sensitivity of the test is 82% and the specificity is 48%.

[3] Catalona WJ, Hudson MA, Scardino PT, Richie JP, Ahmann FR, Flanigan RC et al., Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: Receiver operating characteristic curves. *The Journal of Urology* 1994: 152; 2037-42.

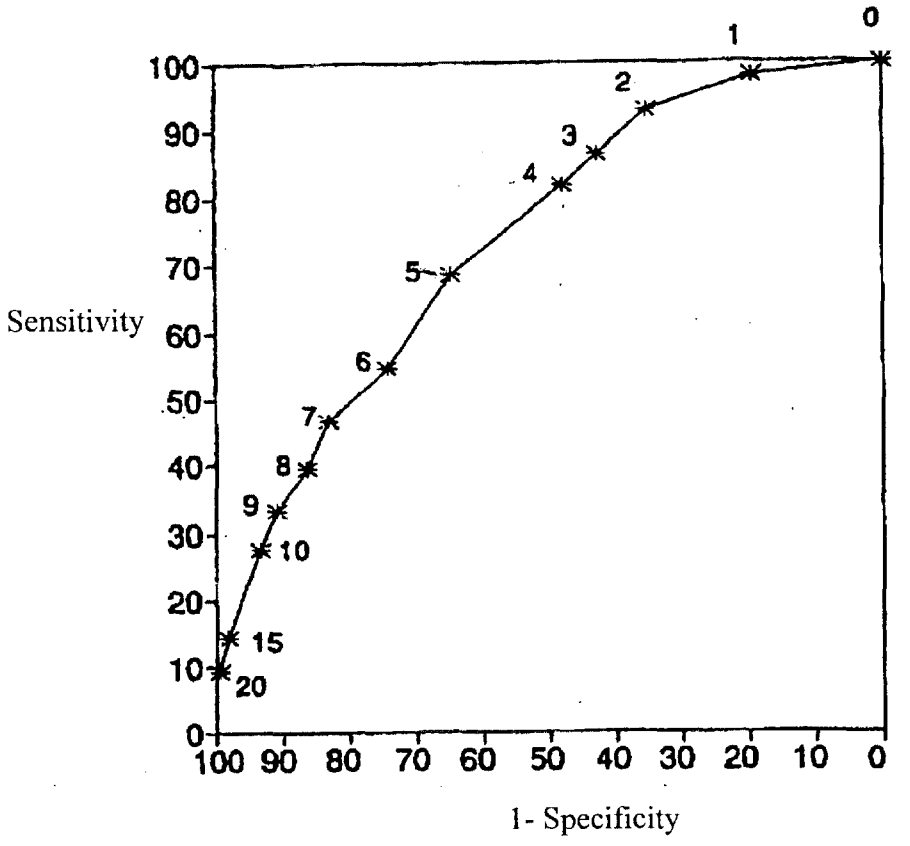

Figure 2. Example ROC Curve: Prostate Specific Antigen (PSA). Test results at PSA levels from 0 to 20 pg/mL are plotted.
Reproduced from Catalona et al., The Journal of Urology, 1994.

1.2.2. Pap Accuracy Study (1): Fahey et al., American Journal of Epidemiology, 1995.

Fahey et al.[1] performed a meta-analysis of 59 cytology studies in order to derive an ROC curve for the Pap smear. The summary ROC curve is reproduced as Figure 3.

This ROC curve shows that a sensitivity of 70% corresponds to a specificity of 70% for cytology. However, the authors of the article point out that since the overall rate of cytology positives is in the range 5-10% in current clinical practice, the specificity is approximately 90-95%, which corresponds on the ROC curve to a sensitivity of only 20-35% for a single test.

Fahey et al. concluded that:

> *"The SROC [Summary Receiver Operating Characteristic] Curve indicates that the Pap test has a low level of accuracy."*

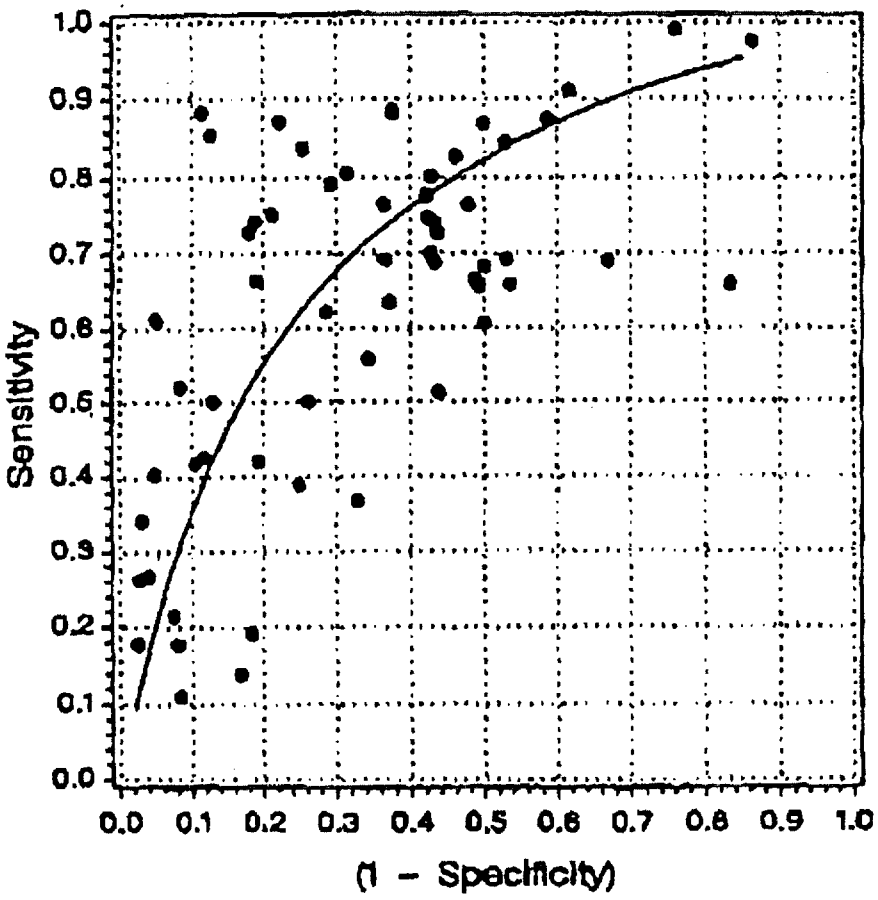

Figure 3. Summary ROC Curve for Cytology
Data points marked are the results of individual studies which satisfied the inclusion criteria for the meta-analysis.
Reproduced from Fahey et al., American Journal of Epidemiology, 1995

1.2.3. Pap Accuracy Study (2): Evidence Report/Technology Assessment: Evaluation of Cervical Cytology. Agency for Health Care Policy and Research, February 1999.

A recent report produced by Duke University, an Evidence-Based Practice Center for the Agency of Health Care Policy and Research (AHCPR)[2] also evaluated the accuracy of conventional cytology screening and compiled a ROC curve from a meta-analysis of available studies. This study concluded that the sensitivity of a single Pap smear may be close to 50%. Overall, the specificity of the test for primary screening was estimated at 98%. However, when the studies which calculated specificity based on an ASCUS/CIN I threshold were considered, the ROC curve showed that a specificity of 90% corresponds to a sensitivity of about 40%, and the quoted cytology sensitivity of 50% corresponds to a specificity of about 85%. This ROC curve is reproduced as Figure 4. The ASCUS/CIN I threshold is the most appropriate for calculating specificity since under current management programs these patients are often referred directly to colposcopy.

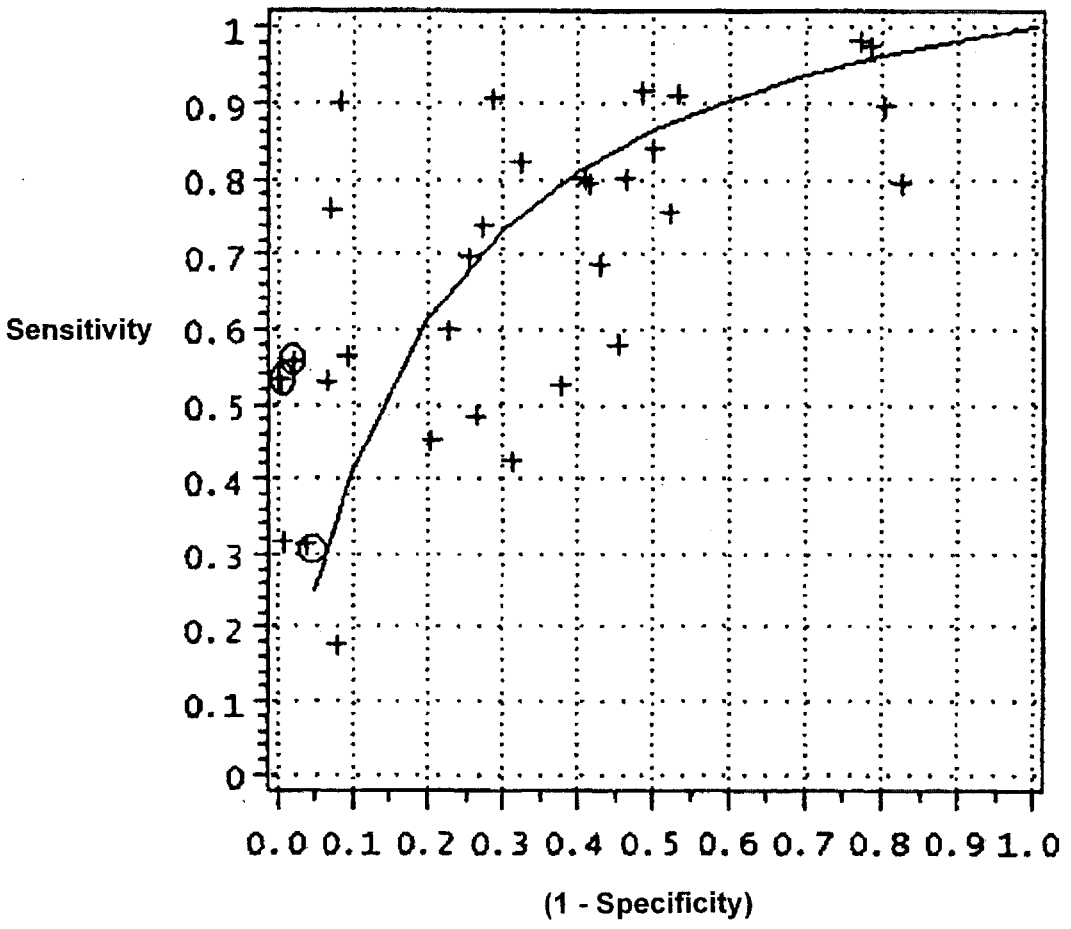

Figure 4. Summary ROC Curve for Cytology
Data points marked are the results of individual studies which satisfied the inclusion criteria for the meta-analysis.
Reproduced from the Duke University/ AHCPR Report, 1999.

The Duke University/ AHCPR researchers concluded that:

> *"Estimates of the sensitivity of the conventional Pap test are biased in most studies; based on the least biased studies, sensitivity [for screening] is near 50 percent, much lower than generally believed."*
>
> and:
>
> *"Future decision models, cost-effectiveness studies and health policy decisions should consider the sensitivity of Pap smear screening close to 50%."*

In summary, the results of the two meta-analyses described in this section are in agreement. Both demonstrate that the sensitivity of cytology is much lower than previously appreciated. Therefore, a summary of the available data shows that the current sensitivity of the Pap smear is of the order of 20-50% for a single test, and the

corresponding specificity is of the order 85-95%. It seems reasonable to conclude that these figures set the appropriate benchmark against which the performance of a new *in vivo* screening device should be evaluated.

SECTION 2. IN-STUDY PAP SMEAR FOR THE TRIAGE INDICATION (INDICATION FOR USE 2)

2.1 Consideration of an *in study* Pap smear

Pages 19 – 21 of the draft document provide FDA guidance for studies for Indication 2 – ASCUS Triage of Triage Following an Abnormal Cervical/Vaginal Cytology Result. The guidance document does not currently include a consideration of whether or not a Pap smear should be performed during the same session as the *in vivo* device examination. We recommend that this be included in the document as a possible study approach. Inclusion of an in study Pap smear would allow a direct comparison between the *in vivo* device and the Pap test, with the two tests performed at the same time. This procedure would eliminate any concerns with respect to the natural regression of lesions in the time between the referral smear and the study session.

2.2 Timeframe between referral smear and study session

On page 19 in the section entitled 'Indications for Use 2 - ASCUS Triage or Triage Following and Abnormal Cervical/Vaginal Cytology Test Result: Description of Patient Population', the document states that 'women with an abnormal ASCUS or higher screening test within the past four weeks are preferred'. Also, on page 20 in the section entitled 'Factors to Consider in Designing the Clinical Study' it is stated that 'patients should have had an ASCUS or higher abnormal cervical/vaginal cytology screening test within the past 4 weeks.'

We suggest that these sections be clarified in order to provide a rationale for this restriction. We presume that the restriction is in place so that if a direct comparison between the results of the referral Pap smear and the *in vivo* device is to be performed in the study, the recent referral smear would still be valid for comparison.

Another approach is to include a second *in study* Pap smear and to use this for a direct accuracy comparison with the *in vivo* device. In this case, the time since the referral smear is of limited relevance since its only function is to affect entry into the study. We therefore suggest that a longer period between the initial referral smear and study enrollment is acceptable and appropriate provided that a second *in study* Pap smear is performed. A period of up to twelve months would seem reasonable.

SECTION 3. FURTHER COMMENTS ON THE GUIDANCE DOCUMENT
(FOUR COMMENTS FOLLOW)

Comment 1. Blinding of Histopathologist(s) to Cytology Results.

On page 17 of the document in the section 'Factors to Consider in Designing a Clinical Study', FDA suggests that the clinician and cytopathologist are blinded to the *in vivo* device results. We recommend that consideration be given to the issue of blinding of the study histopathologist(s), not only to the *in vivo* device results, but also to the results of the *in study* Pap smear (performed during the same session as the *in vivo* device examination), against which the sensitivity and specificity of the *in vivo* device will be compared. Blinding of the histologist(s) to the referral and the *in study* Pap smear results is necessary if an unbiased comparison between the accuracy of the *in vivo* device and the Pap smear is to be performed. This comment is also relevant to the section entitled 'Data Analysis' on page 25, which considers the establishment of a histologic diagnosis in a primary screening study (for Indication 4).

So that patient management is unaffected, two histologists may be required, one following the routine procedure of having access to cytology results during the histological analysis, and another blinded histologist for the purposes of the study.

Comment 2. Recommendation for the Use of Colposcopy in the Derivation of the Reference Diagnosis

We recommend the use of colposcopy in the derivation of the reference diagnosis. A colposcopic reference diagnosis will be required in all cases in which a biopsy is not taken (i.e. in cases where a significant lesion was not visualized colposcopically). The patient diagnosis of *normal* may be obtained by one of two means, as follows:

(A) No significant lesion visualized colposcopically and no biopsy taken, patient classified as normal; or

(B) A lesion is visualized and biopsied, but the histology result is normal, patient classified as normal.

While a colposcopic reference diagnosis will be required for many of those patients finally classified as normal, colposcopic diagnoses can also provide a valuable addition to histologic information at the higher end of the disease spectrum. Expert review of colposcopic videos has diagnostic authority in its own right.

Histology is not an infallible 'gold standard' diagnosis. CIN represents a disease continuum and different histologists will perceive the thresholds between CIN I, II and III slightly differently. Two important studies have been performed in order to assess inter-observer agreement in histology analysis.[4,5] Ismail et al. demonstrated imperfect agreement between the diagnoses of different histologists - for invasive cancer, the kappa index was 0.83, for CIN III (HSIL) - 0.50, for CIN II (HSIL) - 0.18 and for CIN I (LSIL) - 0.17. This agreement is moderately good for CIN III (high grade) lesions but poor for CIN II (high grade) lesions and poor for CIN I (low grade) lesions. Similarly, Robertson et al. concluded in another study that histology inter-observer agreement for high grade lesions was good, but there was 'an inability to distinguish accurately between the lesser grades of CIN'.

We suggest that the following measures are taken to overcome the subjectivity of histology:

* The use of colposcopic video review to check biopsy sites;
* The use of expert review colposcopists to standardize results across centers;
* The use of a semi-objective colposcopic grading system to correlate with the histology results;
* The use of expert pathologists to standardize histology results across centers; and
* The adoption of a consensus approach between colposcopists and pathologists for equivocal cases.

[4] Ismail SM, Colclough AB, Dinnen JS et al., Observer variation in histopathological diagnosis and grading of cervical intraepithelial neoplasia. *British Medical Journal* 1989: 298; 707-10.

[5] Robertson AJ, Anderson JM, Swanson Beck J, Burnett RA, Howatson SR, Lee FD et al., Observer variability in histopathological reporting of cervical biopsy specimens. *Journal of Clinical Pathology* 1989: 42; 231-8.

Comment 3. Age of Subjects

The guidance document suggests exclusion of subjects under the age of 18 for Indications 1 and 4 (pages 17 and 23). We recommend that consideration be given to this age restriction. Subjects under 18 who have previously had a Pap smear should be included in the study provided that the legal guardian has consented. The under-18 age group is an important target population for cervical screening. The exclusion of all subjects under 18 would potentially limit the clinical utility of *in vivo* cervical devices in the future.

Comment 4. Visualization of Endocervical Lesions

On page 24 of the document in the section entitled 'Factors to Consider in Designing Clinical Study', the second bullet point implies that all glandular lesions and adenocarcinomas are to be found exclusively within the endocervical canal. In fact, these lesions can be exclusively ectocervical within the cervical transformation zone or they often have an ectocervical component. These lesions could be detected by a device that visualizes only a part of the endocervical canal - the everted portion visible after speculum insertion. We therefore suggest that the wording of the bullet point is changed, as follows (suggested amendments underlined):

> *"Detection of glandular lesions: The sponsor needs to consider detection of glandular lesions and adenocarcinoma. If the endocervix can not be visualized by the device, even after speculum insertion and opening, there should be a limitation statement in the intended use statement that the in vivo device may not be used to detect those few carcinoma or precursor lesions which are exclusively out of sight within the endocervical canal."*

We thank you for the opportunity to comment on the guidance document and for your consideration of the issues raised in this letter.

Sincerely,

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Regulatory Affairs Manager

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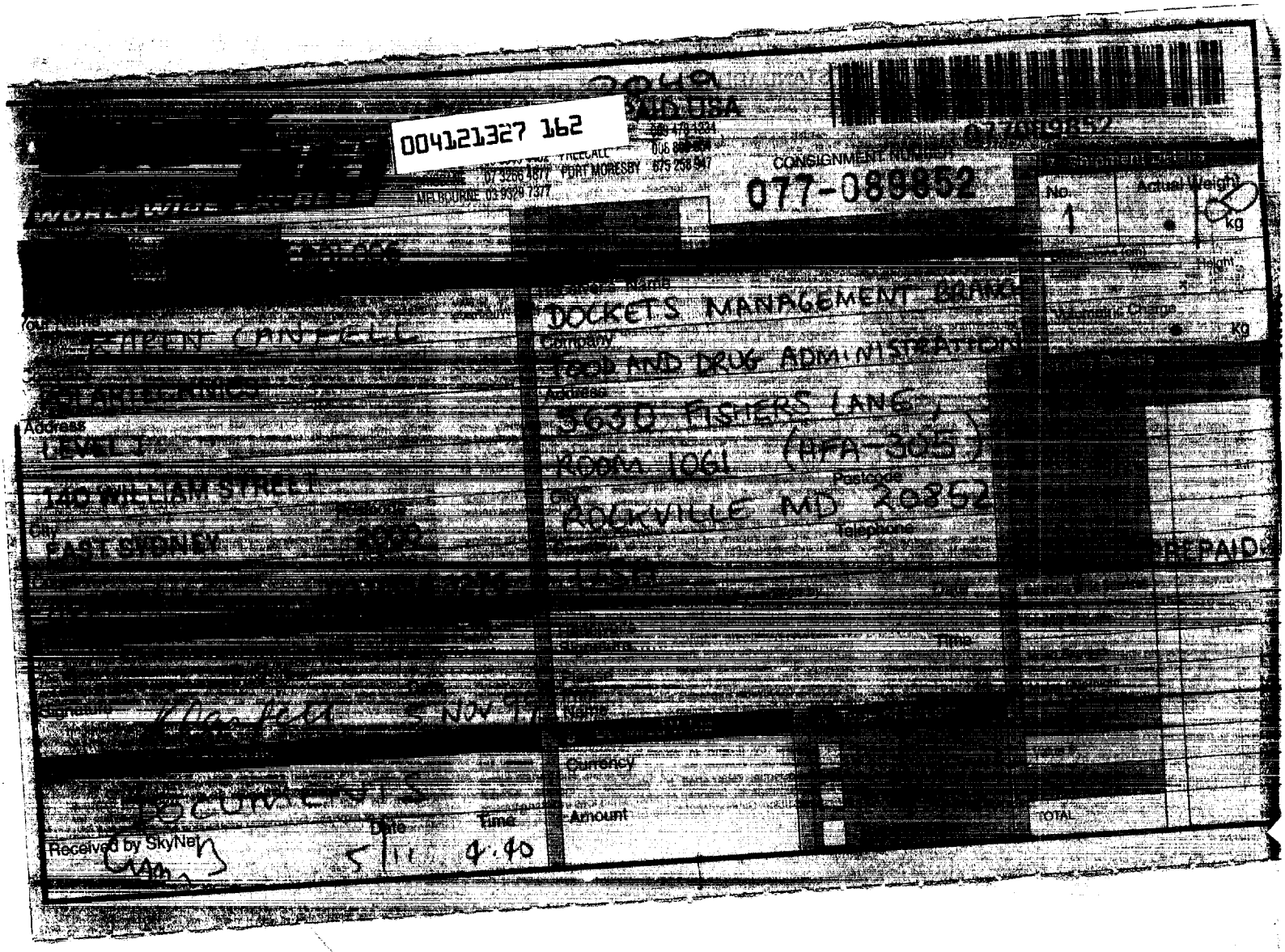
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